

REMARKS

Claims 30-66 were pending in the application. Claims 30, 31, 38, 39, 46, 46, 48, 49, 53, 54, 55, 57, 58, 59, 60, 61, and 63-66 have been amended herein. Support for the amendments to claim 30 can be found at least at claim 30 as previously pending and at paragraph [0022]. Support for the amendment to Claim 31 can be found at least at paragraph [0006], [0022], and [0033]. Support for the amendment to claims 38 and 53 can be found at least at paragraph [0022].

Rejection of claims 30, 31, 34, 38, 45, 46, 48, 49, 53, and 63-66

Claims 30, 31, 34, 38, 45, 46, 48, 49, 53, and 63-66 have been rejected under 35 U.S.C. 103(a) as being obvious over Weiss et al. (US Patent 6,143,293) in combination with Ma (US Patent 6,872,387). This rejection is respectfully traversed.

The Examiner relies on Weiss et al. as teaching a polymer scaffold comprising two or more assembled polymer membranes, wherein each membrane has a surface with varying topology including at least one feature with at least one dimension of about 25-250 microns. The Examiner states that Weiss et al. teaches that the scaffold is made of a polymer material, but does not teach that the polymer material is a hydrogel or a biopolymer hydrogel. The Examiner relies on Ma as teaching a polymer scaffold made of hydrogel polymer. The Examiner states that “all of the claimed elements were known in the prior art and one of ordinary skill in the art at the time the invention was made could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time the invention was made.”

As amended, the pending claims are directed to layered polymer scaffolds comprising a plurality of synthetic biopolymer membranes of from 1 micron to 1 millimeter in thickness which comprise at least one organized feature having at least one dimension of about 10 to 100 microns, wherein said scaffold is microfabricated by a method comprising: generating an elastomer mold; directing a synthetic biopolymer into the mold; curing the synthetic biopolymer in the mold to form a polymer membrane, wherein said membrane comprises a surface with varying topology including at least one feature with at least one dimension of about 10 to 100 microns; removing the cured polymer membrane from the mold; and assembling two or more cured polymer membranes to provide a layered polymer scaffold. The claims are also directed to microfabricated polymer scaffolds comprising at least one membrane, wherein said at least one membrane i) comprises a synthetic biopolymer, ii) is from 1 micron to 1 millimeter in thickness and iii) comprises a surface with varying topology including at least one organized feature with at least one dimension of about 10 to 100 microns.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to apply a flexible teaching, suggestion, or motivation test to combine known elements in order to show that the combination is obvious. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). Importantly, the *KSR* Court noted that “rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” (*In re Kahn*, 441 F.3d 911,988 (CA Fed. 2006) cited with approval in *KSR*).

While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test, the Court acknowledged the importance of identifying “‘a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness determination.” *Id.* (quoting *KSR*,

127 S. Ct. at 1731) (emphasis added). Although the TSM test should not be applied in a rigid manner, it can provide helpful insight to an obviousness inquiry. KSR, 127 S. Ct. at 1731. The KSR Court upheld the secondary considerations of non-obviousness, noting that there is “no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis.” Id. Although the prior art reference, or references when combined, need not teach or suggest all of the claim limitations, a *reason* must be given why the differences between the prior art and the claimed limitation would have been obvious to one of skill in the art (see Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103, Federal Register, Vol. 72, No. 195).

In *KSR* the Supreme Court overturned a holding by the CAFC and found that a claim directed to an electronic car pedal position sensor attached at a fixed pivot point was obvious in view of certain prior art teaching electronic sensors and other prior art teaching an adjustable pedal with a fixed pivot point. The Court held that the CAFC had addressed the question of obviousness in too narrow a manner. Specifically, the Court found the Federal Circuit's analysis to be flawed in three ways. First, the Court held that it is error to look at the prior art with regard only to the specific problem the art was trying to solve, rather any need or problem known in the field and addressed by the art may be examined to provide a reason for combining elements found in the art. Second, the Court held that it is error to assume that a person of ordinary skill in the art attempting to solve a problem will be led only to those prior art elements designed to solve the same problem, rather a person of skill in the art often will be able to fit the teachings of the art together like pieces of a puzzle regardless of the primary purpose behind the teaching of the art. Third, the Court held that it is error to conclude that a patent claim cannot be proved obvious merely by showing the combination of elements was obvious to try, rather “when there is a design need or market pressure to solve a problem and there are a finite number of

identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp."

The technology at issue in KSR was mechanical in nature. The Court stated that "[f]ollowing these principles may be more difficult in other cases than it is here because the claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for improvement." As stated above, the Court found that where "there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp."

The Court also reaffirmed that the *Graham v. John Deere Co.* (383 U.S. 1 (1966)) factors still control an obviousness inquiry. These factors are: 1) "the scope and content of the prior art;" 2) the "differences between the prior art and the claim;" 3) "the level of ordinary skill in the pertinent art;" and 4) objective evidence of nonobviousness. (See *KSR*, 127 S.Ct. at 1734 (quoting *Graham*, 363 U.S. at 17-18)).

KSR has been followed in several Federal Circuit cases. Notably, in *Takada Chemical Industries LTD v. Alphapharm PTY., LTD* (2007 U.S. App. LEXIS 15349 (Fed. Cir. 2007)) technology in the chemical arts is at issue. *Takeda* had claims to pioglitazone, a drug for treating type II diabetes. *Alphapharm* asserted that the claimed compound would have been obvious in view of prior art teaching a structurally similar compound. The CAFC found that the claimed compound was not obvious in view of the art. The Court stated:

[o]ur case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that 'structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions creates a prima facie case of obviousness' Dillon, 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure. In re Grabiak,

769 F.2d 729, 731-32 (Fed. Cir. 1985).

With respect to *KSR*, the court stated that:

[w]hile the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. . . . Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

The court distinguished the facts of the case from those in *KSR* stating:

[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was 'obvious to try.'

As in the case of *Takeda*, in the instant case the Examiner has failed to provide a reason which would have led one of ordinary skill in the art to modify the prior art to arrive at the claimed invention. Similarly, the Examiner has failed to provide a reason why one of ordinary skill in the art would modify the Weiss et al. and Ma disclosures to arrive at the claimed invention.

The Weiss et al. patent discloses methods of making "heterogeneous scaffolds" which are built by mechanical assembly of individual layer or volume elements (column 6, lines 17-

19). These individual elements can be prefabricated using existing scaffold manufacturing processes such as solvent casting, shaping sections with machining, 3D printing, or molded collagen/cell constructs.

These sections can then be mechanically mated using biodegradable or non-biodegradable barbs, pins, screws, clams, staples, wires, string, or sutures.” The Weiss et al. patent further discloses that “[a]ll of the aforementioned assembly strategies can be automated within a CAD/CAM environment, and all assembly can be done within liquid culture media if required.” The CAD/CAM environment refers to computer aided methodologies that allow the design of scaffolds on a relatively large scale. The scaffolds disclosed by Weiss et al. comprise membranes with a minimum of 1mm thickness and are mechanically fastened. It is noted that the smaller dimensions of 25um to 250um referred to by the Examiner reference the scale of the height of the barbs that can be used to mechanically fasten membranes together, not the membranes themselves (see column 8, line 47). The only polymeric scaffold disclosed in the Weiss et al. patent comprises layers of hydroxyapatite, which is a rigid or semi rigid material (column 9, lines 12-13). The Weiss et al. patent fails to disclose scaffolds comprising membranes a surface with varying topology including at least one feature with at least one dimension of about 10 to 100 microns as required by the pending claims.

The Ma patent discloses scaffolds made of natural polymers for use as highly porous scaffolds for cell growth. The scaffolds of the Ma patent are “natural polymers.” The benefits of such natural polymers are disclosed in column 2, lines 3-15 of the patent, which states “[a]lthough synthetic polymers generally give good reproducibility and controlled release kinetics compared to natural materials ... they may not interact with cells in a desired manner. ... On the other hand, natural polymers are advantageous in that they contain information (e.g.,

particular amino acid sequences) that facilitates [sic] cell attachment or maintenance of differentiated function ” The Ma patent fails to teach or suggest scaffolds comprised of synthetic biopolymers such as those presently claimed and, in fact, teaches that such synthetic biopolymers are not desirable. In addition, the components of the scaffolds disclosed by Ma are thicker than the membranes of the present claims. The gels prepared according to the Ma methods were 8 mm in thickness and were cut into 5 slices of the same approximate thickness (see column 6, lines 40-41 of the Ma patent) or 4mm in thickness (column 7, line 23). The methods disclosed by Ma would also fail to yield membranes a surface with varying topology including at least one feature with at least one dimension of about 10 to 100 microns as required by the pending claims.

The Examiner’s rejection appears to be grounded, at least in part, on guidelines set forth in MPEP §2144.06, which states that “it is *prima facie* obvious to combine two or more compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition used for the same purpose ... ”. However, for this conclusion to be valid, the idea of combining the compositions must flow logically from their having been individually taught in the prior art”. *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron); and *Ex parte Quadranti*, 25 USPQ2d 1071 (BAPI 1992) (mixture of two known herbicides held *prima facie* obvious).

In the case of the Weiss et al. and Ma references, there is no motivation present in the references to arrive at the claimed invention. Weiss et al. makes large scale heterogeneous (not uniform) scaffolds which are built by mechanical assembly of individual layer or volume elements in order to facilitate 3-dimensional tissue culture and vascularization (column 5, lines 58-62). Ma makes scaffolds which comprise natural material (an alginate) which are thicker than the membranes of the present claims and are not assembled into higher order scaffolds.

The instantly claimed scaffolds are made on a much smaller scale than those disclosed in Weiss et al. or Ma. Using the methods developed in the instant application, microfabricated polymer scaffolds comprising at least one membrane, which comprises a synthetic biopolymer, are from 1 micron to 1 millimeter in thickness and comprise a surface with varying topology including at least one organized feature with at least one dimension of about 10 to 100 microns can be readily manufactured. Such scaffolds are not taught or suggested in the art.

Moreover, one would not be motivated to combine and/or modify the teachings of Ma to arrive at the claimed invention because the techniques taught by Ma would be intrinsically limited to the materials employed, *i.e.*, alginate. In particular, methods of making alginate scaffolds would be limited by certain features of the materials used, *e.g.*, the hydrophilic character of the alginate, requirement for ionic cross-linking, etc. which would not necessarily be amenable to use with the synthetic biopolymers featured in the instantly amended claims.

Furthermore, absent the micromolding, microfluidic, and spin methodology disclosed in the instant application, there was no reasonable expectation of success that the claimed scaffolds could be made and the prior art methods did not allow for manufacture of scaffolds with the claimed properties. In view of the above amendments and arguments, Applicants respectfully request withdrawal of the instant rejection under 35 U.S.C. §103.

CONCLUSION

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. MITY-001CNRCE.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

Electronic signature: /Debra J. Milasincic, Esq./
Debra J. Milasincic, Esq.
Registration No.: 46,931
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicant